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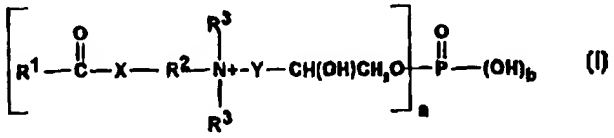

(I)

(57) Abstract

Disclosed are preservative systems useful in aqueous pharmaceutical compositions containing an active agent and a cyclodextrin. The preservative systems comprise boric acid and one or more compounds selected from the group consisting of C_{16} benzalkonium halide compounds, polymeric quaternary ammonium compounds, and quaternary ammonium alkylene glycol phospholipid derivatives of structure (I), where a + b = 3; R^1 is C_8-C_{22} alkyl or alkene; X is NH, O or CH_2; R^2 is C_2-C_6 alkyl; each R^3 is independently C_1-C_{12} alkyl or alkene; and Y is nothing or C_1-C_6 alkyl or alkene; and pharmaceutically acceptable salts thereof.

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PRESERVATIVE SYSTEMS FOR PHARMACEUTICAL COMPOSITIONS CONTAINING CYCLODEXTRINS

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates generally to the antimicrobial preservation of aqueous pharmaceutical compositions. In particular, the present invention relates to the antimicrobial preservation of pharmaceutical compositions containing cyclodextrins.

2. Description of Related Art

Cyclodextrins are known to possess a number of uses in pharmaceutical formulations. For example, cyclodextrins are known to increase the solubility of insoluble or poorly soluble drug compounds, to increase the stability of chemically labile drugs in pharmaceutical formulations, and to increase the comfort or mask the taste of active drugs. See, U.S. Patent No. 4,727,064 (Pitha) and EP 0 149 197 B1 (Janssen Pharmaceutica N.V.).

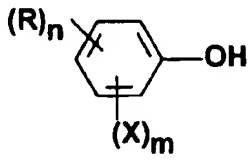
There have been a number of attempts to derivatize cyclodextrins in order to decrease toxicity or increase solubility. For example, hydroxy-propyl-beta-cyclodextrin is a derivative which has been shown to have a relatively low toxicity and a high aqueous solubility as compared to the parent compound, beta-cyclodextrin. In addition to hydroxy-propyl derivative of beta cyclodextrin, a number of other cyclodextrin derivatives are known. See, for example, U.S. Patent Nos. 5,376,645 (Stella et al.) and 4,870,060 (Muller).

Typically, multi-dose pharmaceutical products contain preservatives in order to maintain sterility after opening and during use. Antimicrobial preservation of cyclodextrin-containing formulations can present special problems. For example, Loftsson et al., Drug Development and Industrial Pharmacy, 18 (13), 1477-1484 (1992), have investigated interactions between several commonly us d preservatives and 2-hydroxypropyl-β-cyclodextrin (HPβCD). Loftsson et al. report that the interactions were twofold: (i) the

preservative molecule can displace a drug molecul from the cyclodextrin cavity, thus reducing the solubilizing effects of the cyclodextrin; and (ii) the antimicrobial activity of the pr servative can be reduced by the formation of preservative-cyclodextrin inclusion complexes. Specifically, Loftsson et al. report that chlorobutanol, methylparaben and propylparaben have little or no preservative activity in the tested HPβCD solutions. Additionally, Loftsson et al. found that benzalkonium chloride (with the possible exception of the micro-organism, *Ps. aeruginosa*) and chlorhexidine gluconate did possess significant preservative activity. In contrast, Simpson, FEMS Microbiology Letters, 90, 197-200 (1992), reports that cyclodextrins can inactivate the antimicrobial activity of certain quaternary ammonium compounds. See also, Miyajima et al., Chem. Pharm. Bull., 35(1), 389-393 (1987), regarding the interaction of short-chain alkylammonium salts with cyclodextrins in aqueous solutions, which concluded that α-, β-, and γ-cyclodextrins form complexes with alkylammonium salts having alkyl groups longer than n-butyl, n-hexyl, and n-decyl, respectively.

Benzalkonium chloride (BAC) is the most popular preservative for ophthalmic drug preparations. BAC, as defined in United States Pharmacopeia XIX, is an alkylbenzyldimethyl-ammonium chloride mixture with alkyl chains or homologs beginning with n-C_8H_{17} and extending through higher homologs of C_{10}-, C_{12}-, C_{14}-, and C_{16}-alkyl chains. In our attempts to preserve pharmaceutical formulations containing a cyclodextrin with BAC, however, we have found that cyclodextrin-preservative interactions can significantly reduce or inactivate the preservative efficacy of BAC, when BAC is employed at non-toxic levels.

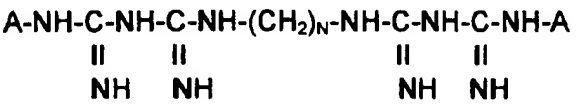
EP 0 119 737 A2 (Takeda Chem. Ind., Ltd.) discloses aqueous pharmaceutical compositions comprising an active ingredient, a cyclodextrin and a phenol derivative as a preservative. The phenol derivative has the formula



where R is alkyl, X is halogen, n is an integer of 0 to 2, and m is an integer of 1 to 3. According to this reference, formulations containing a cyclodextrin and a paraben preservative (methyl-, ethyl-, propyl-, and butylparaben) suffered a significant decrease in the antimicrobial activity of the preservative, while

formulations containing a cyclodextrin and a phenol derivative of the formula abov did not.

JP 60149530 A (Takeda Chem. Ind., Ltd.) discloses aqueous compositions of a principal agent and a cyclodextrin where the compositions contain as a preservative a chlorhexidine derivative of the formula



where A is [independently] (un)substituted phenyl; n is 3-9; and the polymethylene chain may be interrupted by an oxygen atom or an aromatic ring.

JP 01016728 A (Santen Seiyaku KK) discloses antiseptic aqueous preparations containing a drug, a cyclodextrin and a cationic surfactant as a preservative. By adding a cyclodextrin or cyclodextrin derivative, cationic surfactants commonly incompatible with certain drugs can be combined. Disclosed cationic surfactants are benzalkonium chloride, benzethonium chloride or chlorohexidine gluconate. Disclosed drugs include sodium hyaluronate, pilocarpine hydrochloride, lysosyme chloride, Na_2 chondroitin sulfate, glycyrrhetinate, pirenoxine, sodium chromoglycate, and dimethylisopropylazulene sodium sulfate.

JP 6016547 A (Wakamoto Pharm. Co. Ltd.) discloses eye drop compositions containing diclofenac sodium and a water soluble cyclodextrin compound. The reference also discloses that these compositions can be preserved using benzalkonium chloride, benzethonium chloride and chlorhexidine gluconate as cationic surfactants; methylparaben, ethylparaben, propylparaben and butylparaben as parabens; and phenylethyl alcohol and benzyl alcohol as alcohols.

Even if their antimicrobial preservative efficacy is not significantly reduced by interactions with cyclodextrins, benzyl or phenylethyl alcohol and paraben preservatives may present cytotoxicity, evaporation loss, comfort and/or stability problems. Other compounds or systems capable of effectively preserving pharmaceutical formulations containing cyclodextrins are desirable.

SUMMARY OF THE INVENTION

According to the present invention, aqueous pharmaceutical compositions containing a pharmaceutically active compound and a cyclodextrin can be preserved using a preservative system comprising a combination of boric acid and one or more compounds selected from the group consisting of C_{16} benzalkonium halide compounds, polymeric quaternary ammonium compounds, and quaternary ammonium alkylene glycol phospholipid derivatives.

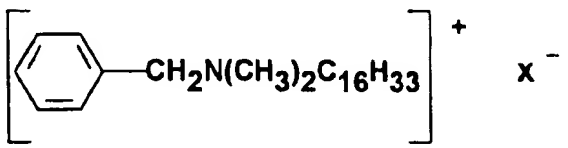
Thus, the present invention relates to aqueous compositions containing a pharmaceutically active drug compound, a cyclodextrin, and a preservative system selected as described above. The present invention also relates to a method of preserving aqueous pharmaceutical compositions containing a cyclodextrin, wherein the method comprises adding to the composition a preservative system of the type described above.

Among other factors, the present invention is based on the discovery that, unlike BAC, C_{16} benzalkonium halide compounds, polymeric quaternary ammonium compounds and quaternary ammonium alkylene glycol phospholipid derivatives do not interact with cylodextrins in a way that significantly reduces or eliminates their antimicrobial preservative activity.

DETAILED DESCRIPTION OF THE INVENTION

The aqueous compositions of the present invention comprise a pharmaceutically active drug compound, a cyclodextrin, and a preservative system, wherein the preservative system comprises a combination of boric acid and one or more compounds selected from the group consisting of C_{16} benzalkonium halide compounds, polymeric quaternary ammonium compounds, and quaternary ammonium alkylene glycol phospholipid derivatives.

The C_{16} benzalkonium halide compounds useful in the compositions of the present invention have the following structure

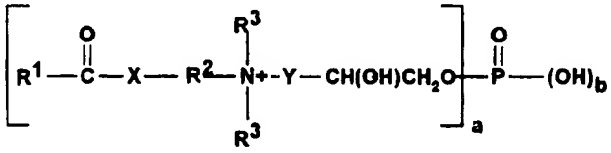


where X = Cl, Br, I, or F. These compounds are known in the art and are either commercially available or can be made using known methods. Th most preferred C_{16} benzalkonium halide compound is C_{16} b nzalkonium chloride. The C_{16} benzalkonium halide compound is typically used in the compositions of the present invention in an amount from about 0.001 to 1%, preferably from about 0.01 to 0.5%. The most preferred concentration of the C_{16} benzalkonium halide compounds in the compositions of the present invention is about 0.02%. (Unless indicated otherwise, all percentages referred to herein are on a w/w basis).

The polymeric quaternary ammonium compounds useful in the compositions of the present invention are those which have an antimicrobial effect and which are pharmaceutically acceptable. The most preferred polymeric ammonium compounds are those known as polyquaternium-1, otherwise known as Polyquad® or Onamer M®, with a number average molecular weight between 2,000 to 30,000. Preferably, the number average molecular weight of the polyquaternium-1 is between 3,000 to 14,000.

The polymeric quaternary ammonium compounds are generally used in the compositions of the present invention in an amount from about 0.001 to about 3%, preferably from about 0.001 to about 0.1%. The most preferred concentration of polymeric quaternary ammonium compounds is about 0.01%.

The quaternary ammonium alkylene glycol phospholipid derivatives useful in the compositions of the present invention include those having the structure



where a + b = 3; R^1 is C_8 - C_{22} alkyl or alkene; X is NH, O, or CH_2; R^2 is C_2 - C_6 alkyl; each R^3 is independently C_1 - C_{12} alkyl or alkene; and Y is nothing or C_1 - C_6 alkyl or alkene. In addition to the acid form of the structure shown above, pharmaceutically acceptable salts of the acid form are also within the scope of present invention. Examples of such salts include the sodium chloride, potassium chloride, and calcium and magnesium salts of the structure shown above. Preferred are the following synthetic phopholipids: cocamidopropyl propylene glycol-dimonium chloride phosphate (sodium chloride salt where R^1 is a coconut oil fatty acid alkyl mixture; X is NH; R^2 is propyl; R^3 is methyl; and Y is CH_2);

borageamidopropyl phosphatidyl propylene glycol-dimonium chloride (sodium chloride salt where R^1 is a boraginaceae oil fatty acid alkyl mixture; X is NH; R^2 is propyl; R^3 is methyl; and Y is CH_2); and cocophosphatidyl propylene glycol-dimonium chloride (sodium chloride salt where R^1 is a coconut oil fatty acid alkyl mixture; X is O; R^2 is propyl; R^3 is methyl; and Y is CH_2). The phospholipid compounds described above can be synthesized using known techniques. The three preferred phospholipids are commercially available from, for example, MONA Industries, Patterson, New Jersey.

The amount of quaternary ammonium alkylene glycol phospholipid derivatives in the compositions of the present invention may range from about 0.01 to about 2%, preferably from about 0.03 to 1.5%. When concentrations approaching the upper limits of these ranges are employed in compositions intended for contact with sensitive tissues, such as topically administrable ophthalmic formulations, the comfort of the compositions may be reduced and additional comfort-enhancing ingredients may be needed (such as emollients typical in the ophthalmic industry: polyethylene glycol, hydroxypropylmethylcellulose, polyvinylalcohol, etc.).

The boric acid used in the compositions of the present invention includes not only boric acid, but also its pharmaceutically acceptable acid addition salts. Accordingly, as used herein, "boric acid" refers to boric acid and its pharmaceutically acceptable acid addition salts. In general, an amount from about 0.3 to about 5% of boric acid is used in the compositions of the present invention. It is preferred to use from about 0.3 to about 3.0%, and it most preferred to use from about 0.5 to about 2.0%.

Suitable cyclodextrins for use in the compositions of the present invention include pharmaceutically acceptable cyclodextrins and cyclodextrin derivatives. Nonionic cyclodextrins are preferred. Most preferred are alkyl derivatives, such as hydroxy-propyl-beta-cyclodextrin. Generally, the concentration of cyclodextrins present in the compositions of the present invention ranges from about 0.5 to about 20%, preferably from about 1 to about 10%.

Any pharmaceutical agent may be included in the compositions of the present invention, particularly both positively-charged and neutral agents (negatively-charged agents may form undesirable complexes with the positively-charged pr servative ingredi nt). For example, pharmaceutical agents which

may be incorporated into the compositions of the present invention include, but are not limited to, the racemic and enantiomeric forms and pharmaceutically acceptable salts, amides, esters and prodrugs of the following types of drugs: adrenocorticoids; glucocorticoids; anticoagulants; anticonvulsants; antidepressants; antidiabetics; antihistamines; decongestants; antithyroid agents; antimuscarinics; etc. Preferred are ophthalmic agents including anti-glaucoma agents, such as carbonic anhydrase inhibitors, prostaglandins and prostaglandin derivatives; anti-inflammatory agents, including but not limited to those classified as aryl- or heteroaryl- alkanoic acids, such as diclofenac, bromfenac, flurbiprofen, suprofen, ketorolac, indomethacin and ketoprofen; anti-bacterial and anti-infective agents, such as sulfacetamide sodium, penicillins and cephalosporins; mydriatic and cycloplegic agents, such as phenylephrine, hydroxyamphetamine, tropicamide; and diagnostic agents such as sodium fluorescein. Combinations of pharmaceutical agents may also be used in the compositions of the present invention.

The aqueous compositions of the present invention may additionally include other pharmaceutically acceptable components. For example, comfort enhancing agents, buffers, surfactants, tonicity agents, antioxidants, chelating agents, binding agents, complexing agents, and viscosity modifying agents, including polymers which will undergo a sol-to-gel transition upon exposure to physical or chemical stimuli, such as changes in pH, ion concentration, and/or temperature, may be added to the compositions of the present invention as desired or as necessary.

The compositions of the present invention may be formulated according to techniques known in the art and administered in a variety of ways. For example, the compositions of the present invention may be formulated for parenteral, oral or topical administration. Topically administrable ophthalmic compositions are preferred.

The following examples are presented to illustrate further various aspects of the present invention, but are not intended to limit the scope of the invention in any respect.

EXAMPLE 1

The following formulations were prepared. In Table 1, below, "BAC" means benzalkonium chloride. "C_{12} BAC" means the C_{12} homolog of benzalkonium chloride (dodecyl benzalkonium chloride). "C_{14} BAC" means the C_{14} homolog of benzalkonium chloride (tetradecyl benzalkonium chloride). "C_{16} BAC" means the C_{16} homolog of benzalkonium chloride (hexadecyl benzalkonium chloride). "HPβCD" means hydroxy-propyl-beta-cyclodextrin.

TABLE 1

	FORMULATION							
Ingredient	A	B	C	D	E	F	G	H
Suprofen	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Boric Acid	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
NaCl	0.7	0.7	0.7	0.7	0.7	0.7	0.6	0.6
Edetate Disodium	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
NaOH/HCl	q.s. pH = 6.5	q.s. pH = 6.5	q.s. pH = 6.5	q.s. pH = 6.5	q.s. pH = 6.5	q.s. pH = 6.5	q.s. pH = 6.5	q.s. pH = 6.5
BAC	0.01	—	—	—	—	0.01	0.01	0.01
C_{12} BAC	—	0.012	—	—	—	—	—	—
C_{14} BAC	—	—	0.012	—	—	—	—	—
C_{16} BAC	—	—	—	0.012	0.015	—	—	—
Hamposyl® L	0.03	0.03	0.03	0.03	0.03	—	0.03	—
Monobasic/Dibasic Na Phosphate	—	—	—	—	—	—	0.1/ 0.03	0.1/ 0.03
HPβCD	2	2	2	2	2	2	—	—
Glycacil	—	—	—	—	—	—	—	—
Polyquaternium-1	—	—	—	—	—	—	—	—
dowicil	—	—	—	—	—	—	—	—
cetrimide	—	—	—	—	—	—	—	—
lysozyme	—	—	—	—	—	—	—	—
phospholipid[1]	—	—	—	—	—	—	—	—

1 = cocamidopropyl PG-dimonium chloride phosphate

TABLE 1 (Continued)

	FORMULATION									
Ingredient	I	J	K	L	M	N	O	P	Q	R
Suprofen	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Boric Acid	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	1.0	0.5
NaCl	0.8	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.3	0.7
Edetate Disodium	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
NaOH/HCl	q.s. pH = 6.5	q.s. pH = 6.5	q.s. pH = 6.5	q.s. pH = 6.5	q.s. pH = 6.5	q.s. pH = 6.5	q.s. pH = 6.5	q.s. pH = 6.5	q.s. pH = 6.5	q.s. pH = 6.5
BAC	0.01	---	---	---	---	---	---	---	---	---
C_{12} BAC	---	---	---	---	---	---	---	---	---	---
C_{14} BAC	---	---	---	---	---	---	---	---	---	---
C_{16} BAC	---	---	---	---	---	---	---	---	---	0.015
Hamposyl® L	---	---	---	---	---	---	---	---	---	---
Monobasic\dibasic Na Phosphate	0.1/ 0.03	---	---	---	---	---	---	---	---	---
HPβCD	---	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
Glycacil	---	0.03	---	---	---	---	---	---	---	---
Polyquaternium-1	---	---	0.01	0.005	---	---	---	---	---	---
dowicil	---	---	---	---	0.03	---	---	---	---	---
cetrimide	---	---	---	---	---	0.01	---	---	---	---
lysozyme	---	---	---	---	---	---	0.1	---	---	---
phospholipid[1]	---	---	---	---	---	---	---	1.5	---	0.03

1 = cocamidopropyl PG-dimonium chloride phosphate

EXAMPLE 2

In addition to the suprofen formulations appearing in Table 1 above, the betaxolol formulations shown in Table 2, below, were also prepared.

Table 2

	FORMULATION		
COMPONENTS	AA	AB	AC
Betaxolol HCl	0.56	0.56	0.56
HPβCD	7.5	7.5	7.5
Boric Acid	0.5	0.5	0.5
Sodium Chloride	0.3	0.3	0.3
EDTA	0.01	0.01	---
BAC	---	0.015	---
Phospholipid[1]	---	---	0.03
POLYQUAD	0.01	---	---
NaOH/HCl QS to pH	7.0	6.6	6.58
Purified Water	QS	QS	QS

1 = cocamidopropyl PG-dimonium chloride phosphate

EXAMPLE 3

The antimicrobial preservative effectiveness of the compositions of Examples 1 and 2 was determined using an organism challenge test according to the methods described in the United States Pharmacopeia (USP) and European Pharmacopoeia (Ph.Eur.). Samples were inoculated with known levels of gram-positive (*Staphyl-ococcus aureus* ATCC 6538) and gram-negative (*Pseudomonas aeruginosa* ATCC 9027 and *Escherichia coli* ATCC 8739) vegetative bacteria, yeast (*Candida albicans* ATCC 10231) and mold (*Aspergillus niger* ATCC 16404) and sampled at specified intervals to determine if the antimicrobial preservative system was capable of killing or inhibiting the propagation of organisms purposely introduced into the formulation. Despite the fact that the compositions of the present invention are not limited to ophthalmic preparations, USP and/or Ph.Eur. preservative efficacy standards for ophthalmic preparations were used for purposes of comparing th antimicrobial activity of the test compositions. As shown in Table 3, an abbr viated time pull schedule was employed. Based on

the data collected, projected pass/fail determinations were mad by comparing the log reductions in the respective organism populations to the standards shown in Table 3.

Table 3

Abbreviated Schedule of Compendial Preservative Effectiveness Requirements for Ophthalmic Compositions

For Bacteria:

	Log Reduction of Organism Population		
Time Pull	USP	Ph.Eur. A (Target)	Ph.Eur. B (Min)
6 hours	-	2	-
24 hours	-	3	1
7 days	3	-	3

For Fungi:

Time Pull	USP	Ph.Eur. A (Target)	Ph.Eur. B (Min)
7 days	-	2	1

- = No requirement at this time pull

The preservative efficacy results for the formulations of Example 1 are shown in Table 4 below, and those for the formulations of Example 2 are shown in Table 5 below.

Table 4

Projected Preservative Efficacy Test Results For Formulations of Example 1

	Log Reduction							Projected Decision		
	6 Hr		24 Hr		Day 7			USP	PhEurA	PhEurB
Formulation	Sa	Pa	Sa	Pa	Sa	Pa	An			
A	0.4	0.4	2.1	1.2	ND	ND	ND	-	F	-
B	0.0	0.1	0.0	0.3	ND	ND	ND	-	F	F
C	0.0	0.1	0.0	0.8	ND	ND	ND	-	F	F
D	5.0	1.3	5.0	2.5	ND	ND	ND	-	F	-
E	5.1	2.7	5.1	3.9	5.1	5.0	4.9	P	P	P
F	0.0	0.3	0.2	0.6	ND	ND	ND	-	F	F
G	2.4	5.0	3.7	5.0	5.0	5.0	ND	P	P	P
G (repeat)	0.4	2.0	2.0	2.2	5.1	2.4	3.9	F	F	F
H	2.5	5.0	4.2	5.0	5.0	5.0	ND	P	P	P
H (repeat)	0.1	1.6	1.4	2.0	3.8	2.4	3.9	F	F	F
I	5.0	3.4	5.0	5.0	5.0	5.0	ND	P	P	P
J	0.2	0.3	0.3	0.4	ND	ND	ND	-	F	F
K	3.4	5.0	3.4	5.0	5.1	5.0	ND	P	P	P
K (repeat)	3.1	5.1	4.0	5.1	5.1	5.1	1.1	P	F	P
K (repeat)*	2.7	5.0	3.8	5.0	5.3	5.0	1.5	P	F	P
L	2.6	5.1	3.7	5.1	5.1	5.1	0.8	P	F	F
M	0.2	3.0	5.1	5.0	ND	ND	ND	-	F	-
N	0.2	2.2	0.2	3.5	ND	ND	ND	-	F	F
O	0.1	0.5	0.1	1.2	ND	ND	ND	-	F	F
P	5.1	5.0	5.1	5.0	5.1	5.0	ND	P	P	P
Q	3.1	5.0	5.3	5.0	5.3	5.0	1.6	P	F	P
Q (repeat)**	4.8	3.6	5.1	5.1	5.1	5.1	1.0	P	F	P
R	5.3	2.1	5.3	3.3	5.3	4.1	5.1	P	P	P

* Boric acid = 1.0%, NaCl = 0.3%
**Boric acid = 0.3%, NaCl = 0.7%
ND = not measured

Table 5

Projected Preservative Efficacy Test Results For Formulations of Example 2

Formulation	Log Reduction							Projected Decision		
	6 Hr		24 Hr		Day 7					
	Sa	Pa	Sa	Pa	Sa	Pa	An	USP	PhEur A	PhEur B
AA	5.3	5.1	5.3	5.1	5.3	5.1	1.8	P	F	P
AB	0.0	2.8	0.1	4.1	1.0	5.1	2.7	F	F	F
AC	0.0	1.8	1.1	4.6	2.4	5.1	2.1	F	F	F

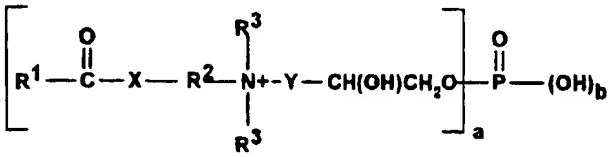
As illustrated in Table 4, formulations containing HPβCD and a preservative system comprising boric acid and a preservative compound selected from the group consisting of C_{16} benzalkonium halide compounds, polymeric quaternary ammonium compounds, and alkylaminopropylene glycol phospholipid compounds (Formulations D, E, K, L, P, Q, and R) possess superior preservative efficacy compared to those formulations containing HPβCD, boric acid, and other preservatives, such as BAC, C_{12}- or C_{14}-benzalkonium chloride, etc. (Formulations A, B, C, F, J, M, N, & O). Formulations G, H & I (all of which contained boric acid and BAC), also performed well in the preservative efficacy assay, but none of these formulations contained HPβCD.

As shown in Table 5, Formulation AA (preservative system = polyquaternium-1 and boric acid) possesses superior preservative efficacy compared to formulation AB (preservative system = boric acid and BAC). Formulation AC (preservative system = boric acid and cocamidopropyl PG-dimonium chloride phosphate) did not meet the preservative efficacy standards, although Formulations P & Q in Table 4 (containing a different active but the same preservative system) were able to meet the efficacy standards.

The invention has been described by reference to certain preferred embodiments; however, it should be understood that it may be embodied in other specific forms or variations thereof without departing from its spirit or essential characteristics. The embodiments described above are therefore considered to be illustrative in all respects and not restrictive, the scope of the invention being indicated by the appended claims rather than by the foregoing description.

WHAT IS CLAIMED IS:

1. An aqueous pharmaceutical composition comprising a therapeutically effective amount of a pharmaceutically active agent, a cyclodextrin and a preservative-effective amount of a combination of boric acid and a preservative compound selected from the group consisting of C_{16} benzalkonium halide compounds, polymeric quaternary ammonium compounds; and quaternary ammonium alkylene glycol phospholipid acid derivatives of the following structure



where a + b = 3; R^1 is C_8 - C_{22} alkyl or alkene; X is NH, O, or CH_2; R^2 is C_2 - C_6 alkyl; each R^3 is independently C_1 - C_{12} alkyl or alkene; and Y is nothing or C_1 - C_6 alkyl or alkene; and pharmaceutically acceptable salts thereof.

2. The composition of Claim 1 wherein the preservative compound is a C_{16} benzalkonium halide and the halide is selected from the group consisting of chloride, bromide, iodide, and fluoride.

3. The composition of Claim 2 wherein the concentration of the preservative compound is from about 0.001 to about 1% (w/w).

4. The composition of Claim 1 wherein the preservative compound is a polymeric quaternary ammonium compound.

5. The composition of Claim 4 wherein the polymeric quaternary ammonium compound is polyquaternium-1.

6. The composition of Claim 5 wherein the concentration of the preservative compound is from about 0.001 to about 3% (w/w).

7. The composition of Claim 6 wherein the concentration of the preservative compound is from about 0.001 to about 0.1% (w/w).

8. The composition of Claim 1 wherein the preservative compound is s lected from the group consisting of cocamidopropyl propylene glycol-dimonium

chlorid phosphate; borageamidopropyl phosphatidyl propylene glycol-dimonium chloride; and cocophosphatidyl propylene glycol-dimonium chloride.

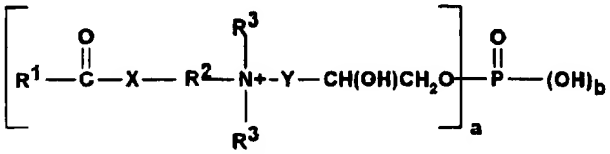
9. The composition of Claim 8 wherein the conc ntration of the preservative compound is from about 0.01 to about 2% (w/w).

10. The composition of Claim 1 wherein the concentration of boric acid is from about 0.3 to about 5 percent by weight.

11. The composition of Claim 1 wherein the concentration of cyclodextrin is from about 0.5 to about 20% (w/w).

12. The composition of Claim 11 wherein the cyclodextrin is hydroxy-propyl-beta-cyclodextrin.

13. A method of preserving an aqueous pharmaceutical composition comprising a therapeutically effective amount of a pharmaceutically active agent and a cyclodextrin wherein the method comprises adding a preservative-effective amount of a combination of boric acid and a preservative compound selected from the group consisting of C_{16} benzalkonium halide compounds, polymeric quaternary ammonium compounds; and quaternary ammonium alkylene glycol phospholipid derivatives of the following structure



where a + b = 3; R^1 is C_8 - C_{22} alkyl or alkene; X is NH, O, or CH_2; R^2 is C_2 - C_6 alkyl; each R^3 is independently C_1 - C_{12} alkyl or alkene; and Y is nothing or C_1 - C_6 alkyl or alkene; and pharmaceutically acceptable salts thereof.

14. The method of Claim 13 wherein the preservative compound is a C_{16} benzalkonium halide and the halide is selected from the group consisting of chloride, bromide, iodide, and fluoride.

15. The method of Claim 13 wherein the preservative compound is a polymeric quaternary ammonium compound.

16. The method of Claim 15 wh rein the polymeric quaternary ammonium compound is polyquaternium-1.

17. The method of Claim 13 wherein the preservative compound is selected from the group consisting of cocamidopropyl propylene glycol-dimonium chloride phosphate; borageamidopropyl phosphatidyl propylene glycol-dimonium chloride; and cocophosphatidyl propylene glycol-dimonium chloride.

18. The method of Claim 13 wherein the concentration of cyclodextrin is from about 0.5 to about 20% (w/w).

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 97/14119

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/00 A61K47/02 A61K47/18 A61K47/24

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CHEMICAL ABSTRACTS, vol. 125, no. 14, 30 September 1996 Columbus, Ohio, US; abstract no. 177471, XP002047729 see abstract & JP 08 175 974 A (LION CORP.,JP) 9 July 1996 ---	1-18
Y	CHEMICAL ABSTRACTS, vol. 125, no. 16, 14 October 1996 Columbus, Ohio, US; abstract no. 204583, XP002047730 see abstract & JP 08 175 985 A (LION CORP.,JP) 9 July 1996 --- -/--	1-18

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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1

Date of the actual completion of the international search	Date of mailing of the international search report
21 November 1997	11/12/1997

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Scarponi, U

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 97/14119

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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